

## Abdominal Ultrasound Findings During and After Treatment of Childhood Acute Lymphoblastic Leukemia

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**Background.** The treatment of acute leukemia in childhood has been increasingly successful. Concurrently, severe leukemia-related gastrointestinal complications have become more common.

**Methods.** We evaluated the findings of the abdominal ultrasound (US) examinations of 52 children with acute lymphoblastic leukemia (ALL) who had severe clinical symptoms indicating infection or abdominal complication during chemotherapy treatment or after the cessation of such treatment and assessed the impact of these findings on patients' subsequent treatment and survival.

**Results.** Our study presents ten cases of typhlitis with a prevalence of 9%, all of which were rapidly diagnosed by US and had a favourable outcome. We also found focal intra-

abdominal parenchymal lesions in six children, five of them due to fungal infection and one due to leukemic infiltration. Several other intra-abdominal pathologies significant for the patients' treatment are also reported.

**Discussion.** We believe that abdominal US is a useful, rapid, safe, and accurate imaging method for children with ALL suspected to suffer from leukemia- or chemotherapy-related gastrointestinal complications. More invasive imaging methods are seldom needed.

**Conclusions.** According to our results, abdominal US gives the necessary information in most of the cases and provides prompt diagnosis, which may prevent possible fatal complications. Med. Pediatr. Oncol. 29:266–271, 1997. © 1997 Wiley-Liss, Inc.

**Key words:** leukemia; ultrasound; abdominal; children; typhlitis; fungal infections

### INTRODUCTION

The treatment of acute leukemia in childhood has been increasingly successful. The long-term event-free survival rates have been improved by using intense treatment regimens, but the risk of treatment toxicity has simultaneously increased. The majority of treatment-related deaths during induction and the first remission in children with acute lymphoblastic leukemia (ALL) are due to infections [1]. Concurrently, severe leukemia-related gastrointestinal complications have become more common. These complications may be fatal, but the prognosis is favorable after a prompt diagnosis and treatment [2]. Ultrasound (US) has turned out to be a good tool for assessing intra-abdominal pathology in leukemic children at the primary stage [3], and it has been suggested to be a rapid, noninvasive and safe imaging method in evaluating different gastrointestinal complications during both the treatment and the follow-up after the cessation of treatment [2,4–7]. Also with severely ill patients, US can be performed at the bedside. The aim of our study was to evaluate the ultrasonic findings of patients with severe clinical symptoms indicating an infection or an abdominal complication during the chemotherapy treatment or the follow-up and to assess the impact of these findings on the patients' treatment and later survival.

### MATERIALS AND METHODS

From December 1980 through April 1992, 108 children with ALL were diagnosed at our institution. During the treatment of ALL or during the follow-up after the cessation of treatment, 120 US examinations were performed on 52 of these children. There were 31 girls and 21 boys aged 1.2–15.3 years (median 4.8 years) at the time of the primary diagnosis. The patients were divided into three risk groups on the basis of the criteria used in all the Nordic countries [8]. Twenty children had a standard risk, twelve an intermediate risk and twenty a high risk, and they were treated according to the Nordic protocol [8–10]. Twenty-one of the patients were treated for one to three relapses. The indications for the 120 US examinations were fever in 68 (57%), abdominal pain in 23 (19%), relapse in 22 (18%) and other symptoms (i.e. icterus, palpable lymph nodes or microscopic hematuria) in 7 (6%) cases. The examinations were performed using HP 77020 AC and Toshiba SSA-270A equipment with

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3.5 MHz and 5 MHz transducers during November 1981 till July 1995. In the ultrasonic evaluation, attention was given to the size of the internal organs, the possible focal lesions in the parenchyma, the presence of ascites, the enlargement of abdominal lymph nodes, and the signs of typhlitis. The criterion of kidney enlargement was a maximum longitudinal axis 2 SD longer than the normal mean [11]. Due to the lack of normal ultrasonic values for hepatic and splenic size in children, the evaluation of size was done subjectively. The normal values for spleen size have been published subsequently [12]. The ultrasonic diagnosis of typhlitis (neutropenic colitis) required thickening of the bowel wall with a characteristic echogenic thickening of the mucosa [4,13]. The normal bowel wall thickness of the colon is  $\leq 3$  mm in adults [4,14], while in children it is usually  $\leq 2$  mm according to our experience, and this was used as the criterion in this study. The ultrasonic features of pancreatitis were diffuse or focal enlargement of the pancreas [15]. The presence of pseudocysts and fluid collections was also evaluated. The medical records were reviewed with special attention to the patients' clinical course, severe clinical symptoms, i.e. fever, septicemia, and abdominal pains.

## RESULTS

In 19 (37%) of the 52 patients the US examination gave information which was significant for the diagnosis or had an impact on the patients' treatment.

### Focal Parenchymal Lesions

Focal parenchymal lesions were found in six children. All of them had focal liver lesions, two had spleen lesions and three kidney lesions. The clinical and patient data of these patients and the appearance of the lesion in US are presented in Table I. One liver lesion was verified as aspergilloma (Fig. 1) by laparotomy and the treatment outcome was favourable. Four of the patients had clinically suspected visceral candidiasis (Fig. 2). In three of these patients the lesions regressed with antifungal medication. One of these cases was fatal. There was one laparotomy-proven focal leukemic infiltration in the enlarged kidney of a patient suffering from relapse. This patient later developed a widespread intra-abdominal mass, clinically due to a leukemic infiltration, which turned out to be fatal.

### Typhlitis

In ten patients US revealed typhlitis (Fig. 3). This gives a prevalence of 9% in all the 108 children with ALL diagnosed during the study period. In all these patients typhlitis was associated with neutropenia, and in three patients it was accompanied by microbiologically verified sepsis. All the patients had fever with or without

abdominal discomfort as the presenting symptom. The clinical and patient data of the patients are presented in Table II. Six patients with typhlitis were having treatment for a relapse. Eight of the ten patients recovered with intravenous antibiotic therapy without any complications. One boy developed an intestinal perforation but recovered with conservative treatment. Another boy had severe intestinal bleeding after the diagnosis of typhlitis, and laparotomy disclosed widespread intestinal candidiasis. This complication was followed by a pancreatic abscess (US-guided fine-needle aspiration disclosed *Enterococcus faecalis*). After antibiotic medication this child finally recovered. Five of the ten survivors of typhlitis eventually died of their underlying disease or other causes.

### Pancreatitis

Three of the patients had pancreatitis due to L-asparaginase treatment. Two of these patients had an edematous pancreas at US. One patient had ascites and a pancreatic pseudocyst, which was treated operatively.

### Organomegaly

Many of the patients showed organomegaly in the course of the treatment or follow-up. Liver enlargement was found in 26 (50%), spleen enlargement in 17 (33%), and kidney enlargement in 13 (25%) of the patients.

### Other Findings

One patient underwent a US examination because of deteriorating liver function tests and relatively mild abdominal symptoms and had an accidental finding of a hypoechoic mass in the perianal space. Surgery revealed a perianal abscess due to *Staphylococcus aureus*. Another patient with mild icterus had slightly dilated intra-hepatic bile ducts during the chemotherapy, without the presence of porta hepatic nodes or enlarged pancreas. This finding was clinically thought to be due to leukemic infiltration.

Five of the children underwent computed tomography (CT) examinations of the abdomen during this study. These CT examinations did not add any significant information compared with the US examinations.

## DISCUSSION

Our findings correspond to the earlier clinical studies which have suggested an increasing tendency for leukemia-related gastrointestinal and abdominal complications. Our study presents ten cases of typhlitis with a prevalence of 9%, which were rapidly diagnosed by US. We also found focal intra-abdominal parenchymal lesions in six children and additionally discovered several other intra-abdominal pathologies significant for the patients' treatment.

TABLE I. Clinical Profile of Patients with Focal Parenchymal Lesions

Patient/Sex/Age at primary diagnosis (years)	Recent chemotherapy P/R	Ultrasonographic findings	Presenting symptoms/ time (years) after primary diagnosis	Method of cytol., histol. or microbiol. confirmation/diagnosis	Clinical diagnosis/patients' outcome
1/F/4.7	HR/R	Hypoechoic solid lesions of the enlarged right kidney	Relapse/4.8	Laparotomy/leukemic infiltration	Leukemic infiltration/regression of the lesion with chemotherapy
		Widespread intra-abdominal hypoechoic mass, focal hypoechoic lesions in the liver	Abdominal pain/6.1	—	Massive leukemic infiltration/exitus, no autopsy performed
2/F/2.4	HR/R	Enlarged liver with focal hypoechoic expansions, enlarged spleen, oedematic pancreas, ascites	Abdominal pain/6.5	Autopsy/candida albicans Abscess in the liver, spleen and kidneys	Visceral candidiasis/exitus
3/M/4.7	SR/P	Hypoechoic lesions surrounded by hypoechoic rim (wheel within wheel) in the liver, hypoechoic expansions of the kidneys, enlarged spleen, ascites	Fever/1.5	FNA/negative	Visceral candidiasis/multiple brain and lung abscesses, regression with antifungal treatment, Subsequent spastic tetraplegia.
4/M/4.6	SR/P	Hypoechoic lesion with small echogenic focuses in the liver	Fever/0.1	Laparotomy/aspergilloma	Aspergillosis in the liver and the lungs/treated operatively and with amphotericin-B, recovery without complications
5/M/5.7	HR/R	Focal hypoechoic lesions in the liver, spleen and kidneys	Fever/4.8	Laparotomy/inflammation Granulomatosa necroticans (spleen)	Visceral candidiasis/regression of lesions with antifungal treatment, recovery without complications. Exitus 7 month later due to sepsis.
6/F/13.6	IR/P	Focal echogenic focus in the liver	Fever/0.6	Sputum and stool culture, Laboratory/candida Esophagitis, stomatitis, Candida parapsilosis sepsis	Visceral candidiasis/regression of lesions with antifungal medication, recovery without complications

Abbreviations: F = Female, M = Male, HR = High risk, IR = Intermediate risk, SR = Standard risk, P = Primary disease, R = Relapse, FNA = Fine needle aspiration.

The etiology of most gastrointestinal complications in leukemic patients is believed to be threefold: primary invasion by leukemic cells (i.e. bowel obstruction, diffuse mucosal ulceration, and hemorrhage, organomegaly, obstruction of biliary, and pancreatic duct system), an altered immune state with profound neutropenia from the leukemia itself and from antileukemic drugs (i.e. opportunistic infections, typhlitis, abscess formation), and direct or indirect gastrointestinal toxic effects of chemotherapy (i.e. hemorrhagic colitis, pancreatitis) [2].

Fungal infections are rapidly becoming the single most serious supportive care problem for children receiving chemotherapy [16]. Invasive fungal infections are most frequently caused by *Candida sp* and *Aspergillus sp*. It is characteristic of systemic candidiasis that fungal abscesses and granulomas are widely disseminated. Hepatic and splenic enlargement is also common. Patients with aspergillosis generally have pulmonary infiltrates [17]. According to the literature, various ultrasonic patterns of hepatosplenic candidiasis have been reported. In

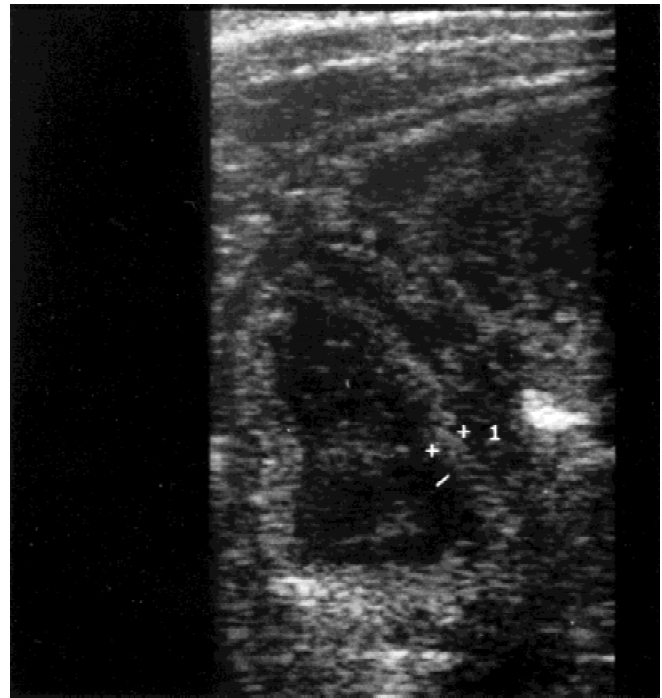


**Fig. 1.** US appearance of aspergilloma in the liver. A large well-defined hypoechoic lesion with multiple scattered small echogenic foci in the liver in four-year-old boy with ALL one month after the beginning of the therapy for the primary disease.



**Fig. 2.** "Wheel within a wheel" lesion in the liver in six-year-old boy with ALL clinically suspected having visceral candidiasis. The lesion regressed with antifungal medication.

the early course of the disease, a "wheel within a wheel" consisting of a peripheral hypoechoic zone representing a ring of fibrosis, an echogenic zone of inflammatory cells and a central hypoechoic nidus correlating with an area of necrosis has been detected [5]. The "bull's eye" lesion lacks the central hypoechoic nidus. The lesion con-



**Fig. 3.** US finding of typhlitis. Transverse scan of the caecum shows wall thickening with characteristic echogenic mucosa (the edematous mucosa measured 4 mm) with 10-year-old boy with ALL during his first relapse.

sists of an inflammatory process making up the echogenic center, which is surrounded by fibrosis producing the hypoechoic rim [6]. Depending on the time of diagnosis during the period of granulocytopenia, hepatosplenic candidiasis may be identified as a pure hypoechoic defect [18]. *Candida* and *Aspergillus* may cause a high-level echogenic foci with variable degrees of posterior acoustic shadowing. Histologically, this phenomenon represents either extensive fibrosis or focal fibrinous exudates [19]. We found one patient with aspergillosis and four with visceral candidiasis. The patient with aspergillosis and three of the patients with candidiasis had a favourable outcome due to prompt treatment. Most of the fungal lesions were hypoechoic at US. One patient with candidiasis had a high-level echogenic focus in the liver. Another patient with clinically suspected candidiasis showed "wheel within wheel" lesions in the liver. In our series, US was diagnostic in all of the cases clinically suspected as having visceral involvement. No other imaging methods of the abdomen, such as computed tomography or magnetic resonance imaging, were needed to confirm the diagnosis.

Typhlitis [20], also termed neutropenic enterocolitis [21] or ileocecal syndrome [22], is an infection of the bowel occurring in patients with profound neutropenia. The frequency of typhlitis has increased recently [23]. Probably the most plausible explanation is the aggressiveness of the modern chemotherapy regimens. Typhlitis in



TABLE II. Clinical Profile of Patients With Typhlitis

Patient/Sex/Age at primary diagnosis (years)	Recent chemotherapy P/R	Presenting symptoms/time (years) after primary diagnosis	Outcome
1/F/4.9	HR/P	Fever/0.4	Recovery without complications
2/F/4.9	SR/P	Fever and abdominal pain/2.3	Recovery without complications
3/F/1.4	HR/R	Fever/3.2	Recovery without complications
4/M/13.4	HR/R	Fever/1.9	Typhlitis cum sepsis and proctitis recovery without complications
5/M/5.7	HR/R	Fever/4.5	Recovery without complications
6/M/14.4	HR/R	Fever/2.3	Perforatio intestinalis, Recovery with conservative treatment
7/F/6.4	HR/R	Fever/7.3	Recovery without complications
8/F/4.0	IR/P	Fever/0.5	Recovery without complications
9/M/4.0	HR/R	Fever/4.0	Severe intestinal hemorrhage, laparotomy, Visceral candidosis, pancreatic abscess, Final recovery
10/F/2.3	HR/P	Fever/0.1	Recovery without complications

Abbreviations: F = Female, M = Male, HR = High risk, IR = Intermediate risk, SR = Standard risk, P = Primary disease, R = Relapse.

the absence of chemotherapy is rare, but may occur prior to the administration of chemotherapy [24]. Typhlitis involves antineoplastic agent-induced damage to the intestinal mucosa, primarily in the terminal ileum, ascending colon and cecum, and generally occurs when these patients are neutropenic after administration of chemotherapy. Bacterial invasion of the bowel wall occurs with a variable inflammatory response. It may progress to full-thickness infarction and perforation of the intestine [25]. Typhlitis is characterized by fever, abdominal pain, and tenderness during periods of neutropenia. US has turned out to be a useful tool in diagnosing typhlitis [4,13,26]. US can show wall thickening in these patients [4], who have a characteristic thickened, echogenic mucosa [13]. Our study presents 10 patients with typhlitis diagnosed clinically and with US. None of our cases were fatal in contrast to the previously reported [23] higher mortality rates. We believe that ultrasound provides an accurate, rapid, safe, and noninvasive diagnostic method for typhlitis. By using US in the early phase of the disease, potential fatal complications can be avoided.

Pancreatitis is one of the reported complications related to L-asparaginase treatment in children with ALL [27]. US has proven to be helpful in the diagnosis of early subclinical and established L-asparaginase-related pancreatitis [7]. Secondary complications such as pancreatic pseudocyst, ascites, focal fluid collections and pleural fluid are easily detected by ultrasound. The three patients with L-asparaginase-induced pancreatitis in our series had positive findings in US.

Some of the focal visceral lesions and the diffuse organ enlargement may be due to leukemic infiltration [28,29]. The presence of abdominal organomegaly is a common finding in children with ALL, especially in patients with a hematologically active disease associated with an extramedullary leukemic burden [3]. Massive invasion by leukemic cells may cause bowel, biliary, and

pancreatic duct obstruction [2]. Leukemia may also infiltrate the portal tracts and the parenchyma with permeation of the sinusoids causing ductal stasis [30]. This might be an explanation in the case of one of our patients with icterus. Leukemic cellular infiltrations of the liver, spleen, or kidneys have been noted at autopsy in approximately 50% of leukemic patients with complete bone marrow and meningeal remission [31]. Organomegaly may also be present without leukemic infiltration [29] and may sometimes be due to fungal infection [17]. Our study included one biopsy-proven case of leukemic infiltration of the kidney. This patient with leukemic relapse later developed widespread intra-abdominal infiltration leading to exitus. We detected diffuse organomegaly of undefined origin in several patients in our study, both during hematologically active disease and during complete remission. The significance of this phenomenon remains unclear.

## CONCLUSIONS

We conclude that abdominal US is a noninvasive, rapid, and accurate imaging method for children with ALL. US can also be performed at the bedside when necessary. It provides the information needed for the diagnosis and treatment of leukemia- or chemotherapy-related gastrointestinal complications. According to our experience, more invasive imaging methods are seldom needed.

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